Review The Eurasian Journal of Medicine EAJM 2013; 45: 47-9

# Tissue Damage and Oxidant/Antioxidant Balance

## *Doku Hasarı ve Oksidan/Antioksidan Denge*

Abdullah Kisaoglu[1], Bunyamin Borekci[2], O. Erkan Yapca[3], Habib Bilen[4], Halis Suleyman[5]

[1]Department of General Surgery, Faculty of Medicine, Ataturk University, Erzurum, Turkey
[2]Department of Obstetrics and Gynecology, Faculty of Medicine, Ataturk University, Erzurum, Turkey
[3]Department of Obstetrics and Gynecology, Sorgun State Hospital, Yozgat, Turkey
[4]Department of Endocrinology and Metabolism, Ataturk University Faculty of Medicine, Erzurum, Turkey
[5]Department of Pharmacology, Faculty of Medicine, Ataturk University, Erzurum, Turkey

## Abstract

The oxidant/antioxidant balance in healthy tissues is maintained with a predominance of antioxidants. Various factors that can lead to tissue damage disrupt the oxidant/antioxidant balance in favor of oxidants. In this study, disruptions of the oxidant/antioxidant balance in favor of oxidants were found to be a consequence of the over-consumption of antioxidants. For this reason, antioxidants are considered to be of importance in the prevention and treatment of various types of tissue damage that are aggravated by stress.

**Key Words:** Antioxidant, Ischemia, Oxidant

## Özet

Sağlıklı dokularda oksidan/antioksidan denge antioksidanların üstünlüğüyle sürdürülür. Doku hasarına yol açabilecek çeşitli agresif faktörler oksidan/antioksidan dengenin oksidanların leyhine bozulmasını sağlar. Bu derleme çalışmasında, oksidan/antioksidan dengenin oksidanlar leyhine bozulmasının, antioksidan sistemlerin aşırı harcanmasına bağlı olarak geliştiği rapor edilmiştir. Bu nedenle oksidatif strese bağlı çeşitli doku hasarının önlenmesinde ve tedavisinde antioksidanların önemli olduğu anlaşılmaktadır.

**Anahtar Kelimeler:** Antioksidan, İskemi, Oksidan

The oxidant/antioxidant balance in healthy tissues is maintained with a predominance of antioxidants [1]. A disruption of this balance causes tissue damage. This state is termed oxidative stress [2]. The occurrence of tissue damage is determined by the oxidant/antioxidant balance [3]. The oxidant/antioxidant balance changes in favor of oxidants in various damage models created in living tissues, and decreases in antioxidant levels are observed, whereas the oxidant levels increase [4]. Uzar et al. [5] reported decreases in the total antioxidant level and increases in the oxidant level in the context of brain ischemia-reperfusion damage. The levels of free oxygen radicals increase and the levels of antioxidants decrease depending on the level of consumption of antioxidants in tissues affected by traumatic brain damage. Increasing levels of free oxygen radicals due to the consumption of antioxidants cause lipid, protein and DNA oxidation [6-8]. An oxidant/antioxidant imbalance in favor of oxidants has also been reported in the context of brain damage caused by radiation [9]. Free oxygen radicals are regarded as the major cause of myocardial ischemia-reperfusion injury [10, 11]. Ischemia and post-ischemia reperfusion may lead to the production of free oxygen radicals in the lungs as well [12, 13]. Endothelial cells and type II pneumocytes play important roles in the formation of free radicals in the lungs [14]. The mechanisms of oxidative damage in the lungs caused by ischemia and hypoxia are different. It is argued that an oxidative damage independent of the depletion of ATP stores occurs during oxidative stress related to pulmonary ischemia. The accumulation of hypoxanthine, output product of rapid ATP catabolism, increases during hypoxia [13, 15, 16]. The damage caused by ischemia-reperfusion in many organs, such as the brain, heart, lungs, liver and intestines, has been investigated, and free radicals were found to be one of the major components of ischemia-reperfusion damage [17-22]. Tok et al. [23] reported that the levels of oxidant indicators such as MDA and MPO increased, whereas the levels of antioxidant indicators such as GSH and GST decreased. Yiğiter et al. [24] reported an increase in the MDA level and a decrease in the GSH level in kidney tissues with damage related to ureter ligation. In addition, Yiğiter et al. [24] found an increase in the amount of 8-OH-Gua, a product of DNA oxidation, in damaged kidney tissue.

Evidence of severe histopathological damage in ovary tissue in which the level of MDA was higher has been obtained by experimental studies on the prevention of ischemia-

**Received:** November 5, 2012 / **Accepted:** December 8, 2012

**Correspondence to:** Halis Suleyman, Department of Pharmacology, Faculty of Medicine, Ataturk University, 25240, Erzurum, Turkey
Phone: +90 442 231 65 58 Fax: +90 442 236 09 68 e-mail: halis.suleyman@gmail.com

doi:10.5152/eajm.2013.08

reperfusion damage [25]. Kurt et al. [26] histopathologically showed that damage occurs in the ovary tissue of rats when oxidant levels are high. Isaoglu et al. [27] reported a significant increase in the levels of oxidants-compared with the levels in the healthy group-in ovary tissue in which only ischemia occurred. Increases in the levels of oxidant indicators and decreases in the levels of antioxidant indicators have also been observed in ovaries damaged by drugs [28].

Derin et al. [29] showed that damage is related to increases in lipid peroxidation and decreases in PGE2 in gastric tissue affected by ischemia-reperfusion. Moreover, Derin et al. [29] reported that L-carnitine prevents gastric damage by repressing lipid peroxidation and increasing the decreased PGE2 level. It has been reported that carnitine, a powerful antioxidant, prevents damage caused by lipid peroxidation in the spinal cord, retina, kidneys, heart and brain [30-34]. Non-steroidal anti-inflammatory drugs (NSAIDs) used for treatment are also known to cause damage to gastric tissue [35]. NSAIDs not only decrease PG synthesis but also increase the levels of free oxygen radicals in the gastric mucosa. The decrease in PG synthesis leads to increases in neutrophil activation and their production capacity of free radicals and to tissue damage [36]. Free oxygen radicals may react with macromolecules in cells and cause serious cell damage, such as lipid peroxidation, oxidative modifications of proteins and DNA oxidation [37-39].

It is known that antioxidant treatment is useful to prevent tissue damage related to increases in oxidant production. In addition to preventing radical formation prior to damage, antioxidants also repair the existing oxidative damage, neutralize various reactive by-products and degrade oxidized biomolecules [40]. Consequently, it is believed that oxidants play an important role in the development of tissue damage, and antioxidants are important in the prevention and treatment of such damage.

**Conflict of interest statement:** The authors declare that they have no conflict of interest to the publication of this article.

## References

1. Clarkson PM, Thompson HS. Antioxidants: What role do they play in physical activity and health? Am J Clin Nutr 2000; 72: 637-46.
2. Yeum KJ, Russell RM, Krinsky NI, Adlini G. Biomarkers of antioxidan capacity in hydrophilic and lipophilic compartments of human plasma. Arch Biochem Biophys 2004; 430: 97-103.
3. Aguilar A, Alvarez-Vijande R, Capdevila S, Alcoberro J, Alcaraz A. Antioxidant Patterns (Superoxide Dismutase, Glutathione Reductase, and Glutathione Peroxidase) in Kidneys From Non- Heart-Beating-Donors. Transplantation Proceedings 2007; 39: 249-52.
4. Iraz M, Ozerol E, Gulec M, et al. Protective effect of caffeic acid phenethyl ester (CAPE) administration on cisplatin induced oxidative damage to liver in rat. Cell Biochem Funct 2006; 24: 357-61.
5. Uzar E, Acar A, Firat U, et al. Protective effect of caffeic acid phenethyl ester in rat cerebral ıschemia/reperfusion damage. Turk Norol Derg 2011; 17: 131-6.
6. Bayir H, Kagan VE, Borisenko GG, et al. Enhanced oxidative stress in iNOS-deficient mice after traumatic brain injury: support for a neuroprotective role of iNOS. J Cereb Blood Flow Metab 2005; 25: 673-84.
7. Chong ZZ, Li F, Maiese K. Oxidative stress in the brain: Novel cellular targets that governsurvival during neurodegenerative disease. Prog Neurobiol 2005; 75: 207-46.
8. Shao CX, Roberts KN, Markesbery WR, Scheff SW, Lovell MA. Oxidative stress in head trauma in aging. Free Radic Biol Med 2006; 41: 77-85.
9. Eşmekaya MA, Sırav B, Ozer C, Seyhan N. Effects of radiofrequency radiation on brain tissue oxidant and antioxidant levels in rats. Gazi Med J 2011; 22: 100-4.
10. Lefer DJ, Granger DN. Oxidative stress and cardiac disease. Am J Med 2000; 109: 315-23.
11. Dhalla NS, Elmoselhi AB, Hata T, Makino N. Status of myocardial antioxidants in ischemia-reperfusion injury. Cardiovasc Res 2000; 47: 446-56.
12. Kelly RF. Current strategies in lung preservation. J Lab Clin Med 2000; 136, 427-40.
13. Zhao G, Al-Mehdi AB, Fisher AB. Anoxia-reoxygenation versus ischemia in isolated rat lungs. Am J Physiol 1997; 273: 1112-7.
14. Al-Mehdi AB, Shuman H, Fisher AB. Intracellular generation of reactive oxygen species during nonhypoxic lung ischemia. Am J Physiol 1997; 272: 294-300.
15. Fisher AB, Dodia C, Tan ZT, Ayene I, Eckenhoff RG. Oxygen-dependent lipid peroxidation during lung ischemia. J Clin Invest 1991; 88: 674-9.
16. Eckenhoff RG, Dodia C, Tan Z, Fisher AB. Oxygen-dependent reperfusion injury in the isolated rat lung. J Appl Physiol 1992; 72: 1454-60.
17. Harton JW, Walker PB. Oxygen radicals, lipid peroxidation and permeability changes after intestinal ischemia and reperfusion. J Appl 1993; 74: 1515-20.
18. Bilbao G, Contrenas JL. Reduction of ischemia reperfusion injury of the liver by vivo adenovirus mediated gene transfer of the antiapoptotic Bcl-2 gene. Ann Surg 1999; 230: 185-93.
19. Weight SC, Bell PR, Nicholson ML. Renal ischemia reperfusion injury. Br J Surg 1996; 83: 162-70.
20. Collard CD, Gehran S. Phatophysiology, clinical manifestations and prevention of ischemia reperfusion injury. Anest 2001; 94: 1122-38.
21. Carden DL, Granger DN. Phatophysiology of ischemia reperfusion injury. J Pathol 2000; 190: 255-66.
22. Chamoun F, Burne M, O'Donnell M, Rabb H. Phatophysiologic role of selectins and their ligands in ischemia reperfusion injury. Front Bioscl 2000; 5: 103-9.
23. Tok A, Sener E, Albayrak A, et al. Effect of mirtazapine on oxidative stress created in rat kidneys by ischemia-reperfusion. Ren Fai 2012; 34: 103-10.
24. Yigiter M, Yildiz A, Polat B, et al. The protective effects of metyrosine, lacidipine, clonidine, and moxonidine on kidney damage induced by unilateral ureteral obstruction in rats. Surg Today 2012; 42: 1051-60.

25. Ingec M, Isaoglu U, Yilmaz M, et al. Prevention of ischemia-reperfusion injury in rat ovarian tissue with the on-off method. J Physiol Pharmacol 2011; 62: 575-82.
26. Kurt A, Isaoglu U, Yilmaz M, et al. Biochemical and histological investigation of famotidine effect on postischemic reperfusion injury in the rat ovary. J Pediatr Surg 2011; 46: 1817-23.
27. Isaoglu U, Yilmaz M, Calik M, et al. Biochemical and histopathological investigation of the protective effect of disulfiram in ischemia-induced ovary damage. Gynecol Endocrinol 2012; 28: 143-7.
28. Salman S, Kumbasar S, Yilmaz M, et al. Investigation of the effects of the chronic administration of some antihypertensive drugs on enzymatic and non-enzymatic oxidant/antioxidant parameters in rat ovarian tissue. Gynecol Endocrinol 2011; 27: 895-9.
29. Derin N, Izgut-Uysal VN, Agac A, Aliciguzel Y, Demir N. L-carnitine protects gastric mucosa by decreasing ischemia-reperfusion induced lipid peroxidation. J Physiol Pharmacol 2004; 55: 595-606.
30. Akgun S, Tekeli A, Kurtkaya O, et al. Neuroprotective effects of FK-506, L-carnitine and azathioprine on spinal cord ischemia-reperfusion injury. Eur J Cardiothorac Surg 2004; 25: 105-10.
31. Kocer I, Kulacoglu D, Altuntas I, Gundogdu C, Gullulu G. Protection of the retina from ischemia-reperfusion injury by L-carnitine in guinea pigs. Eur J Ophthalmol 2003; 13: 80-5.
32. Onal A, Astarcıoglu H, Ormen M, Atila K, Sarioglu S. The beneficial effect of L-carnitine in rat renal ischemia-reperfusion injury. Ulus Travma Derg 2004; 10: 160-7.
33. Atila K, Coker A, Sagol O, et al. Protective effects of carnitine in an experimental ischemia-reperfusion injury. Clin Nutr 2002; 21: 309-13.
34. Calvani M, Arrigoni-Martelli E. Attenuation by acetyl-L-carnitine of neurological damage and biochemical derangement following brain ischemia and reperfusion. Int J Tissue React 1999; 21: 1-6.
35. Kourounakis PN, Tsiakitzis K, Kourounakis AP, Galanakis D. Reduction of gastrointestinal toxicity of NSAIDs via molecular modifications leading to antioxidant anti-inflammatory drugs. Toxicology 2000; 144: 205-10.
36. Wallace JL. Mechanisms of nonsteroidal anti-inflammatory drug (NSAID) induced gastrointestinal damage-potential for development of gastrointestinal tract safe NSAIDs. Can J Physiol Pharmacol 1994; 72: 1493-8.
37. Niki E, Yamamoto Y, Komuro E, Sato K. Membrane damage due to lipid oxidation. Am J Clin Nutr 1991; 53: 201-5.
38. Mitch WE, Goldberg AL. Mechanisms of muscle wasting. The role of the ubiquitinproteasome pathway. N Engl J Med 1996; 335: 1897-905.
39. Cuzzocrea S, Reiter RJ. Pharmacological action of melatonin in shock, inflammation and ischemia/reperfusion injury. Eur J Pharmacol 2001; 426: 1-10.
40. Sorg O. Oxidative stres: a theoretical model or biological reality? C R Biologies 2004; 327: 649-62.